

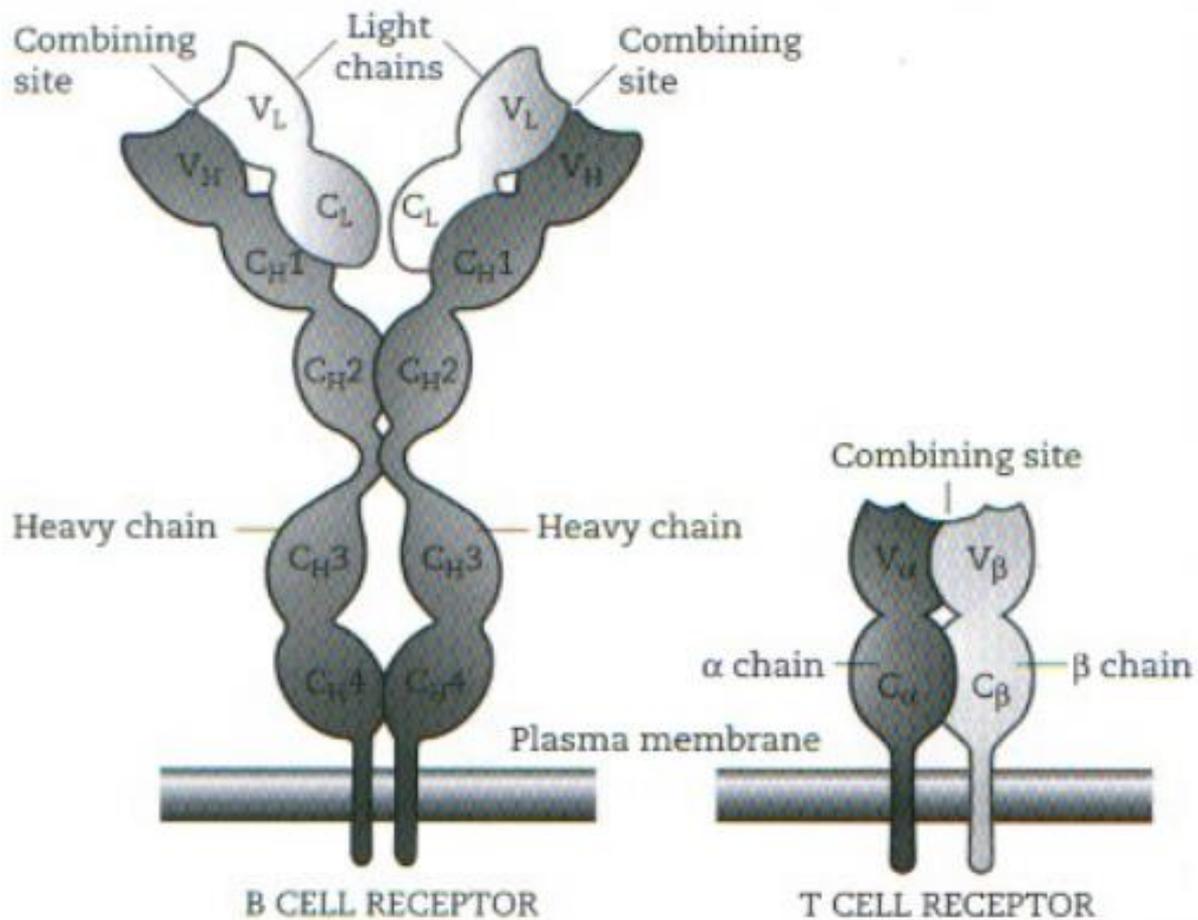
Biology of T-cells and antigen presentation

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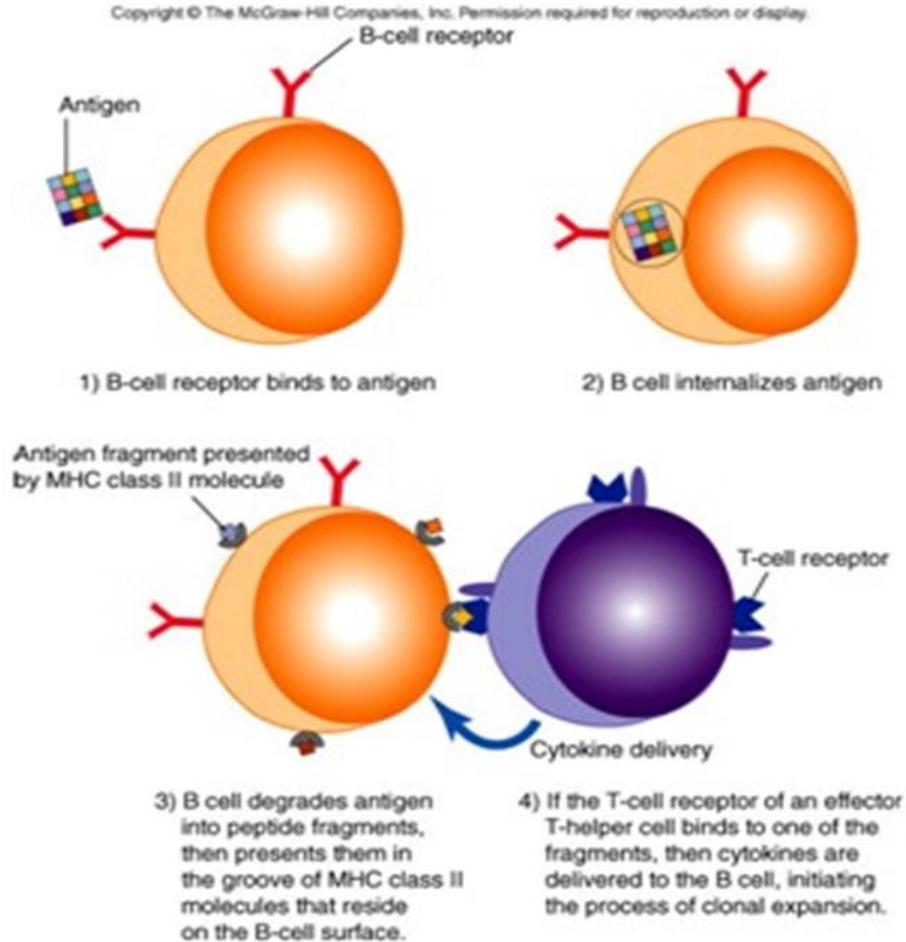
Adaptive Immunity

- T and B cells activation, Proliferation and differentiation

B & T CELL RECEPTORS

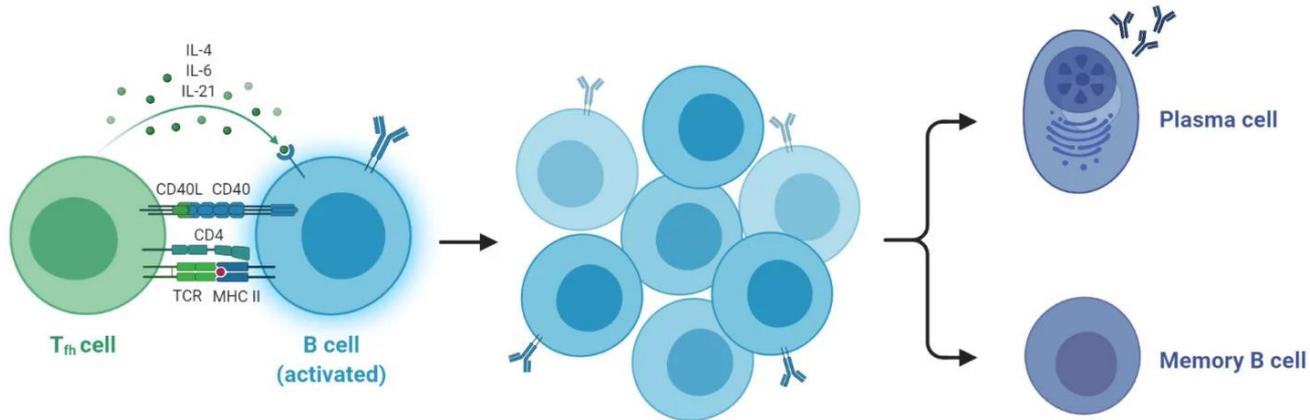
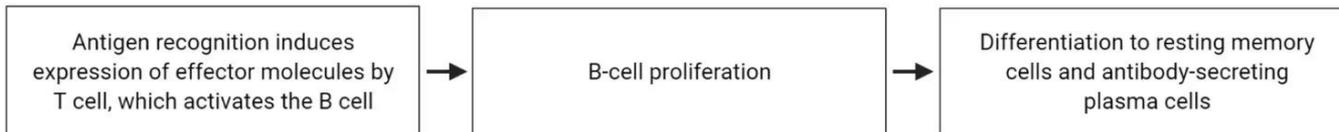


B cells activation in follicle center



B cells differentiation

Steps in B-cell Differentiation



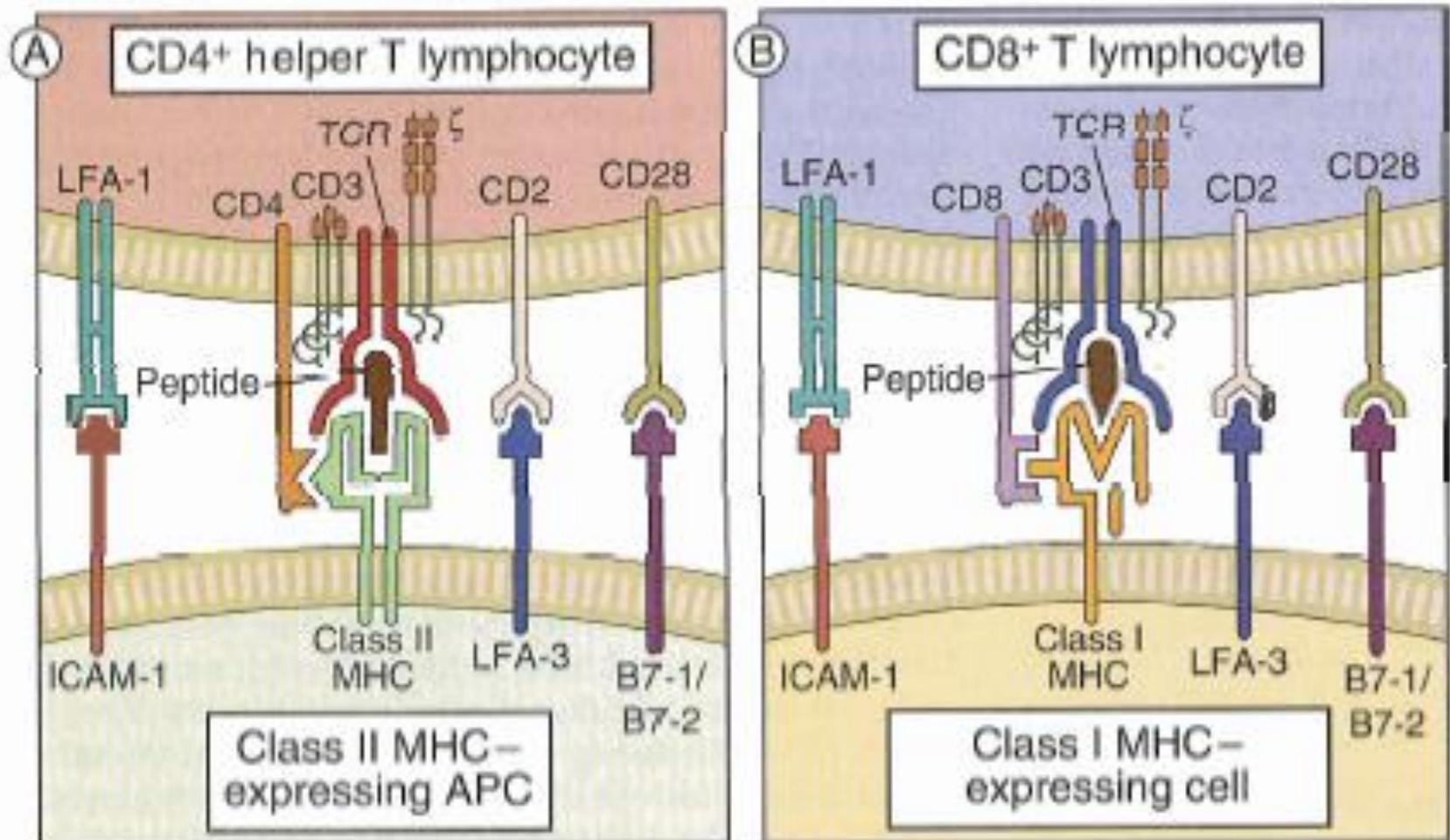
The 
Biology
Notes

The 
Chemistry
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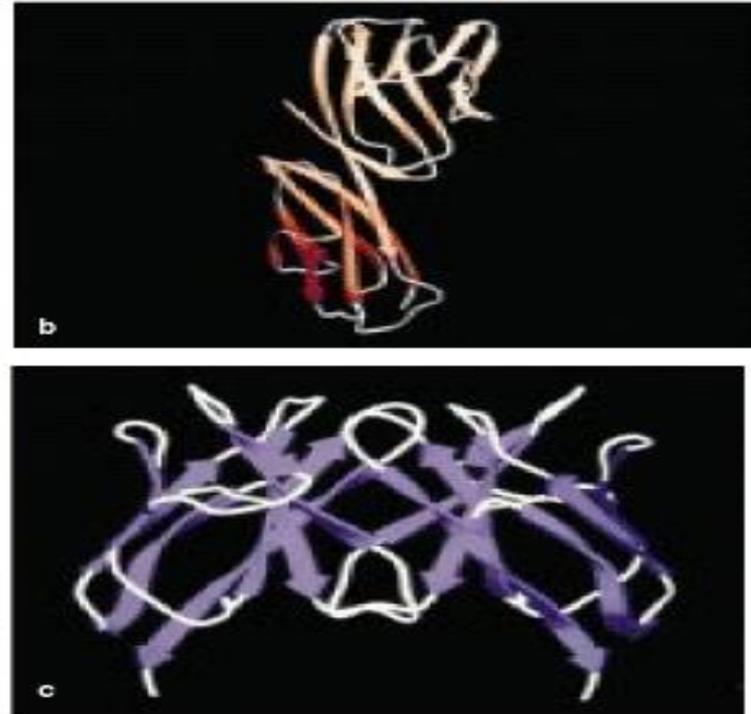
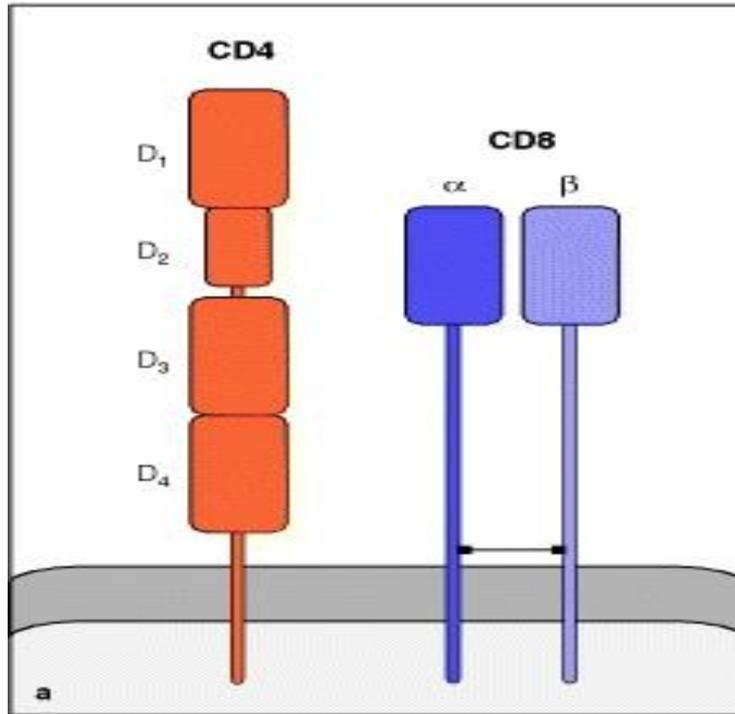
T cells activation in paracortex in lymph nodes or the periarteriolar lymphoid sheath in the spleen



Factors influencing the Strength binding of the TCR to antigen

- **first signal**
- (TCR bind antigen and CD4/8 binding to MHC).
- Coreceptors binding;
 - **T cells coreceptors** are the CD4 and CD8 proteins (Th or Tc respectively). CD8 and CD4 interact with class I and class II MHC molecules, respectively.
 - These besides co-receptors CD3 and zeta chain do signal transduction to inside T cells

CD4 and CD8

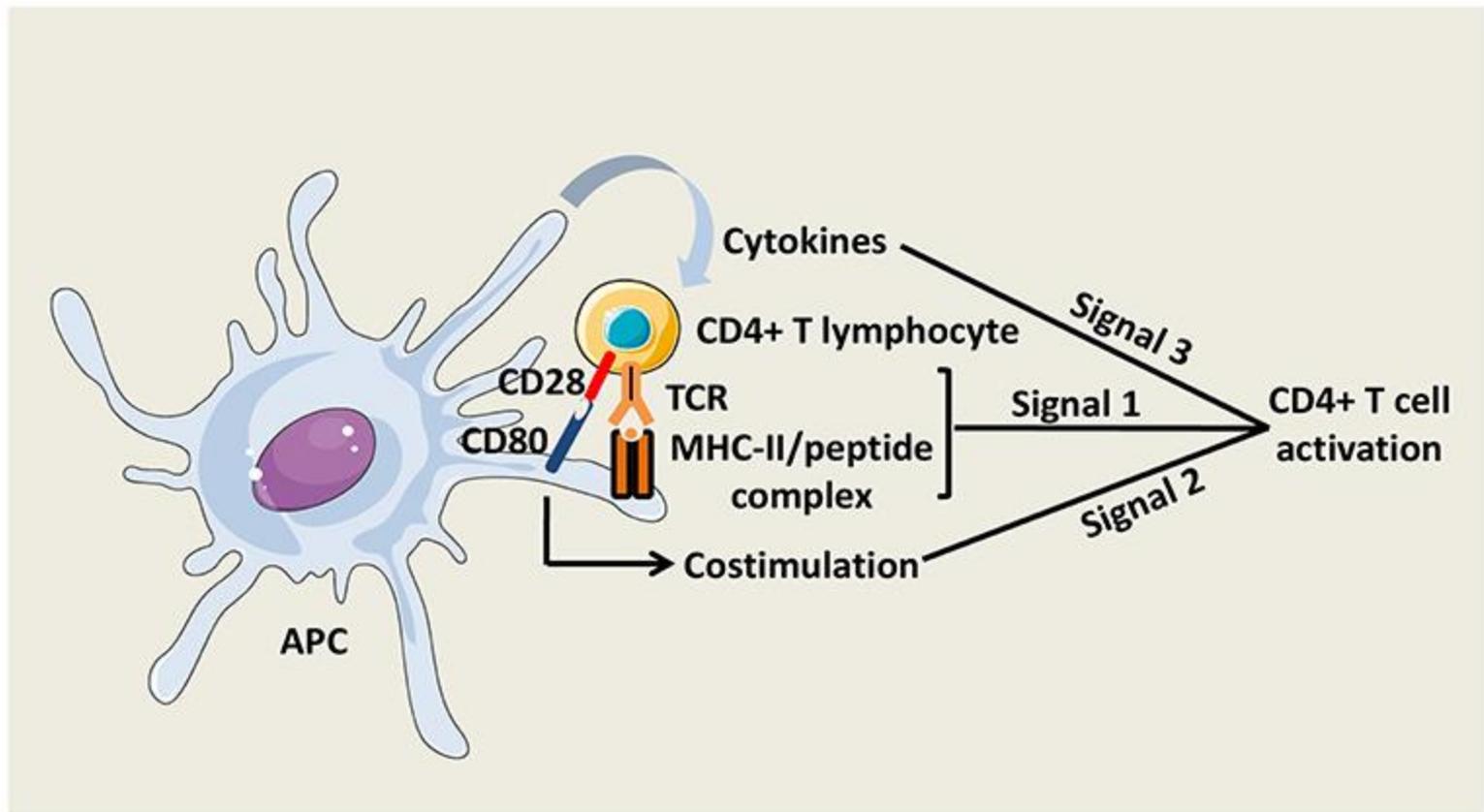


- Cluster of differentiation (CD) are proteins expressed on T cells (CD4 or CD8) have a role in binding the MHC and used to differentiate the cells by binding to monoclonal antibodies. CD8 T cells are T_c, CD4 T cell is Th1 or Th2

Costimulatory receptors on T cells

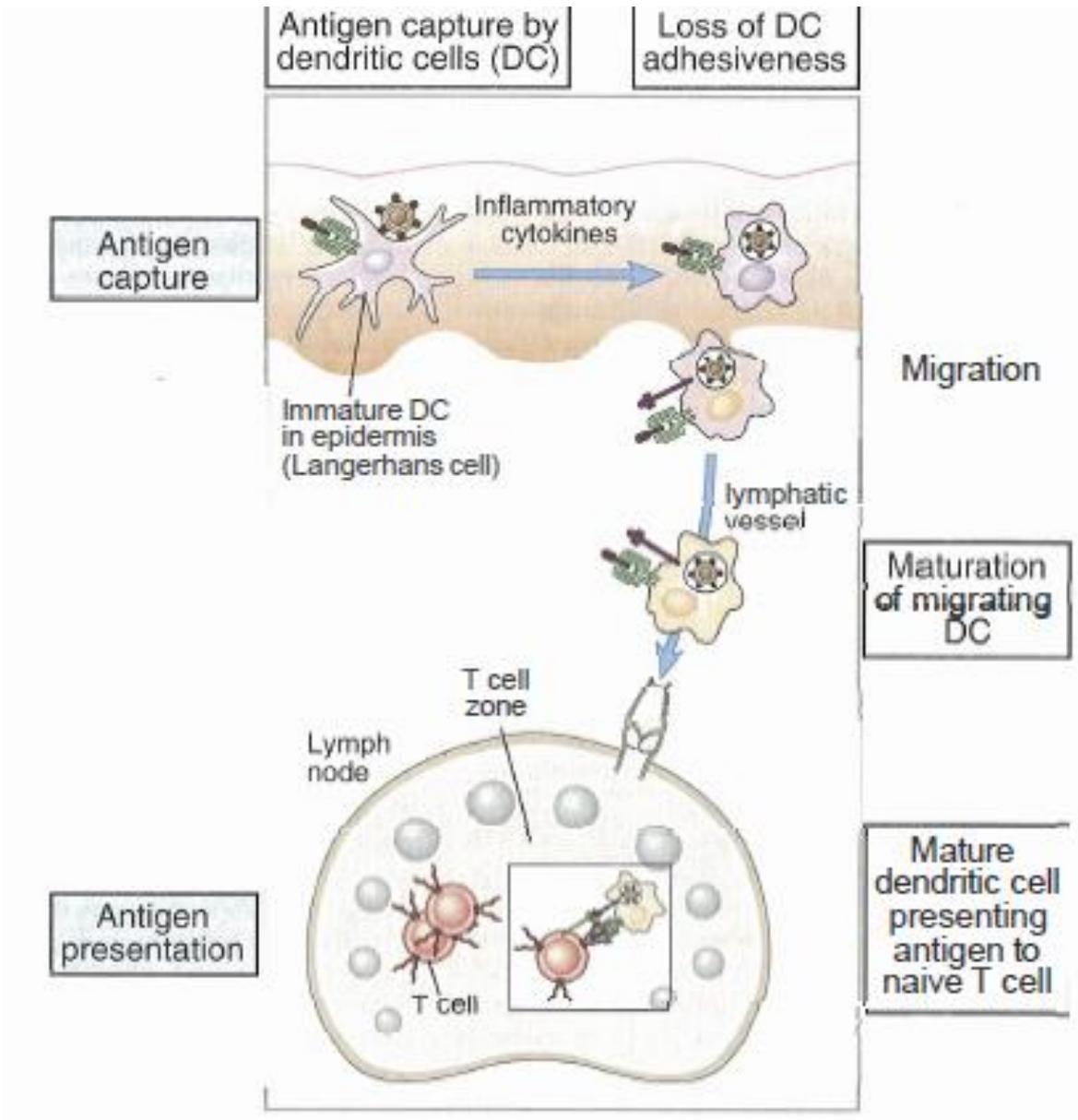
- Provide so-called **second signals** for lymphocytes
 - CD28, the earliest accessory molecules induce signaling. when it bind B7 on APC, it initiate T cell proliferation by expression of IL-2 cytokine and its receptor.
 - when the antigen is cleared CTLA-4 replaces CD28 on T cell and bind B7 on APC. So that T cell is regulated, lead to T cell death.
 - CD2 is a glycoprotein present on more than 90% of mature T cells, and on NK cells. The principal ligand for CD2 in humans is a molecule called leukocyte function associated antigen 3 (LFA-3, or CD58), CD2 functions as a signal transducer
 - CD40L---CD40 on B cells (important for activation and isotype switch of B cells,)

- **Signal 3**, cytokine effect; T cells proliferation by the effect of IL-2 (growth factor from T cell to act on itself and on B cells)
- If one of these is absent-----T cell anergy and tolerance
- If all present-----T cell proliferation and differentiation to effector and memory cells
 - Effector cell in CD4 cells is T h1 , Th2 or Th17 lymphocyte
 - Effector cell in CD8 cells is always cytotoxic T lymphocyte (CTL).



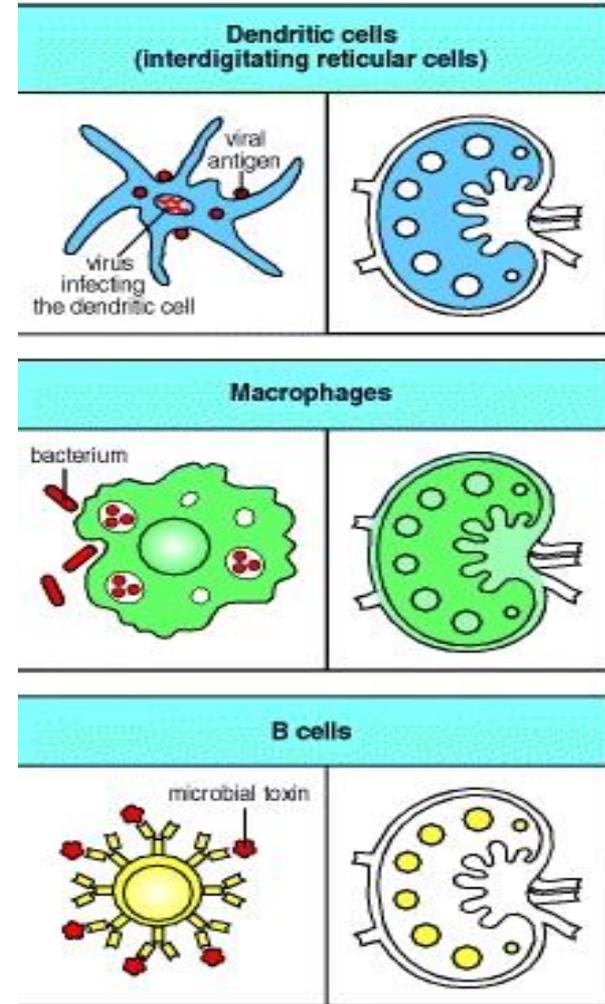
- T cells involved in
 - Defense against intracellular and extracellular pathogens (Tc in cell mediated immunity and Th help in humoral immunity)
 - Tumor immune response
 - Graft rejection
 - Autoimmune diseases

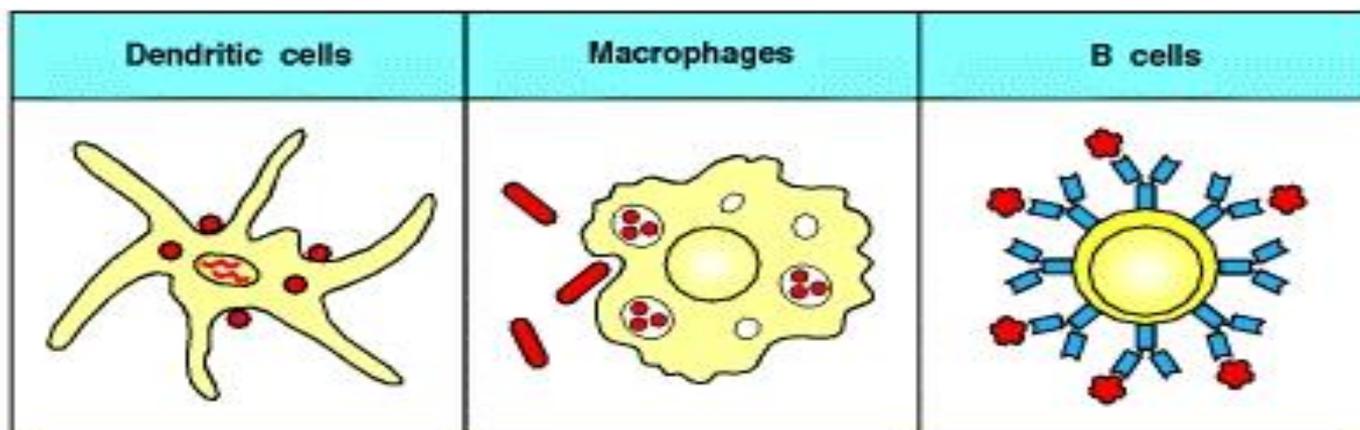
- Immunoglobulin superfamily includes the antigen receptors of T and B cells, CD3, the co-receptors CD4, CD8, most Fc receptors, CD28 and B7 adhesion molecules, cytokine receptors and the MHC molecules.



APCs

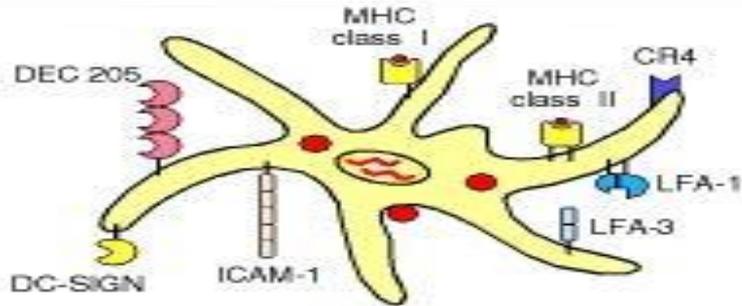
- **Antigen-presenting cells are distributed in tissues, blood and in the lymph node**
- Dendritic cells, Macrophages and B cells
- Mature dendritic cells are by far the most important activators of naive T cells and activated by wide range of antigens (viral, Bacterial and allergens)
- B cell bind soluble intact antigen and present it to TH by MHC2



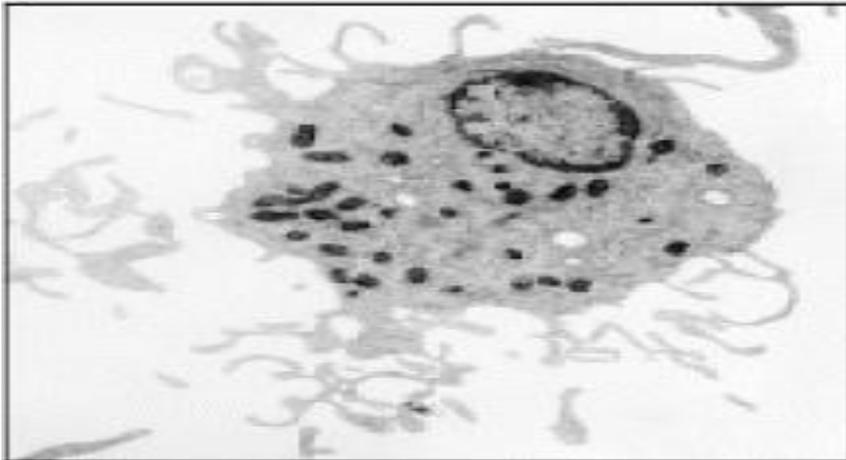
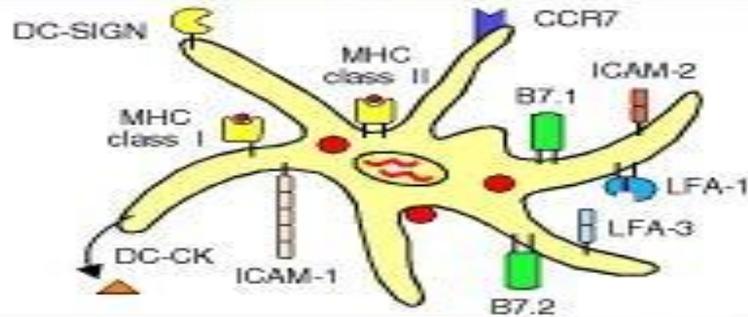


Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines - to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible - to +++	Inducible - to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Lymphoid tissue Connective tissue Epithelia	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

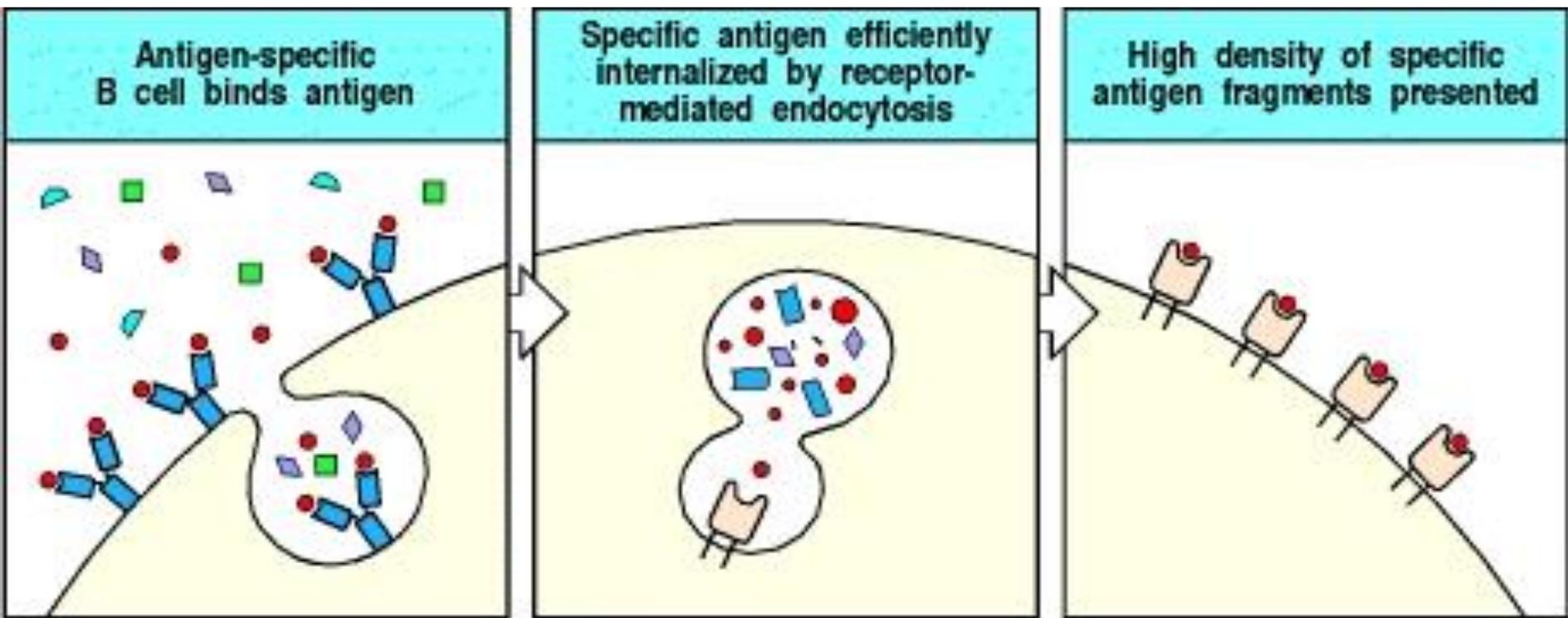
Immature dendritic cells in peripheral tissues



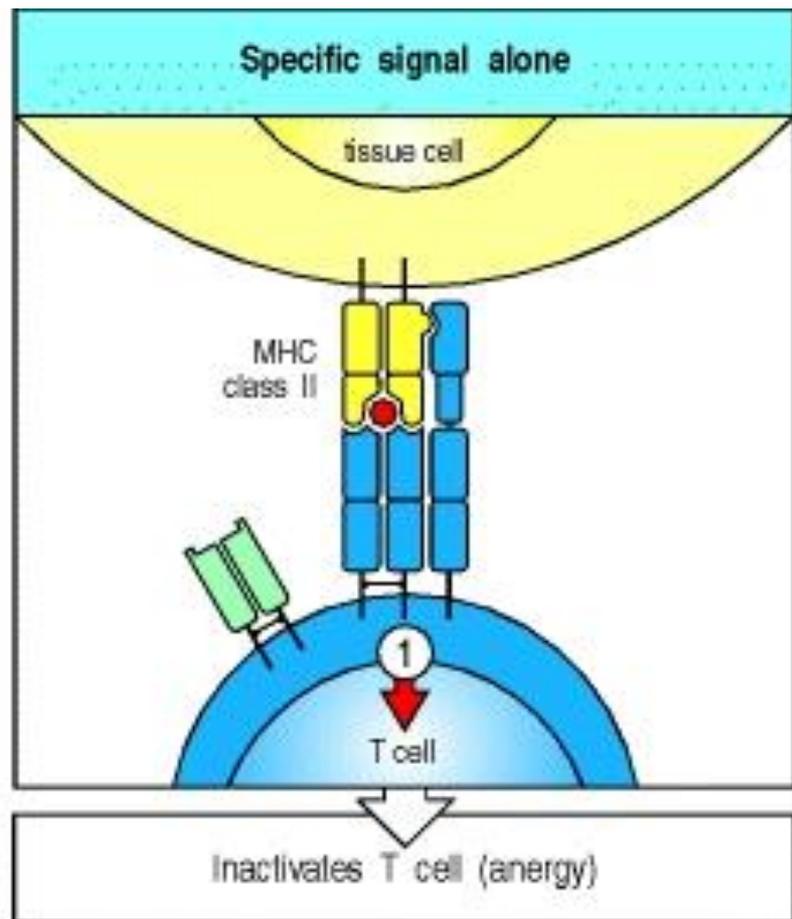
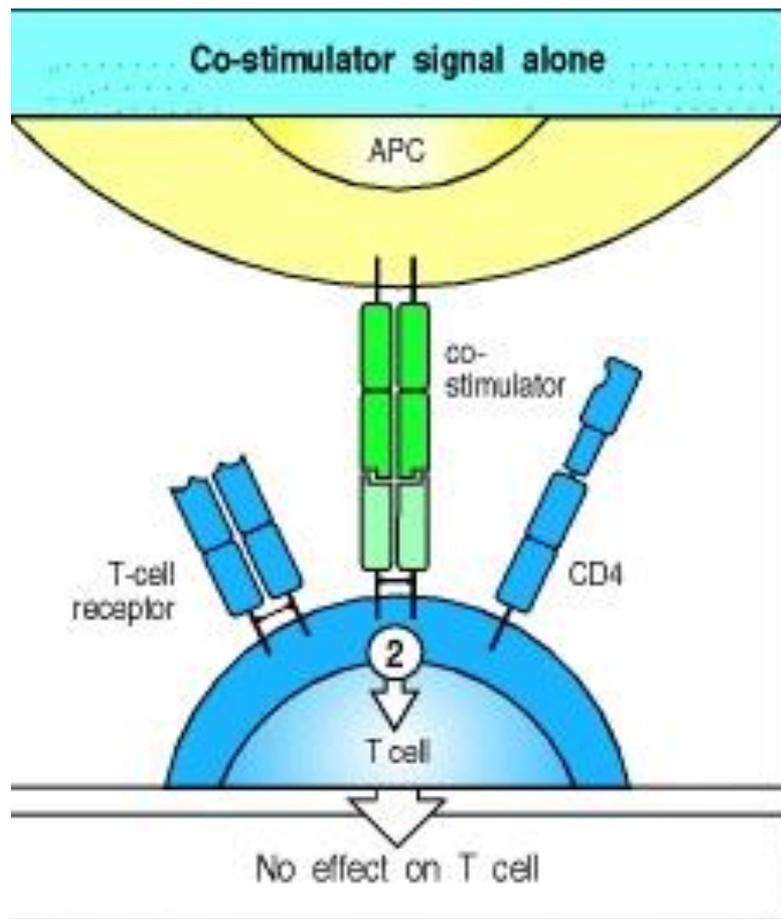
Dendritic cell in lymphoid tissue



- Immature dendritic cells, exist at tissues and sites of infection, they express low levels of MHC1 & 2 and phagocytic receptor PRR, but low adhesion molecules.
- Internalization occur as a result of binding the Ag with PRR or by macropinocytosis.
- After engulfing the pathogen they become mature DC; migrate to peripheral L.N.
 - lose their phagocytic activity
 - and express more adhesion molecules, MHC and co-stimulatory molecules,
 - secrete chemotactic factors to attract naïve T cells to the LN.

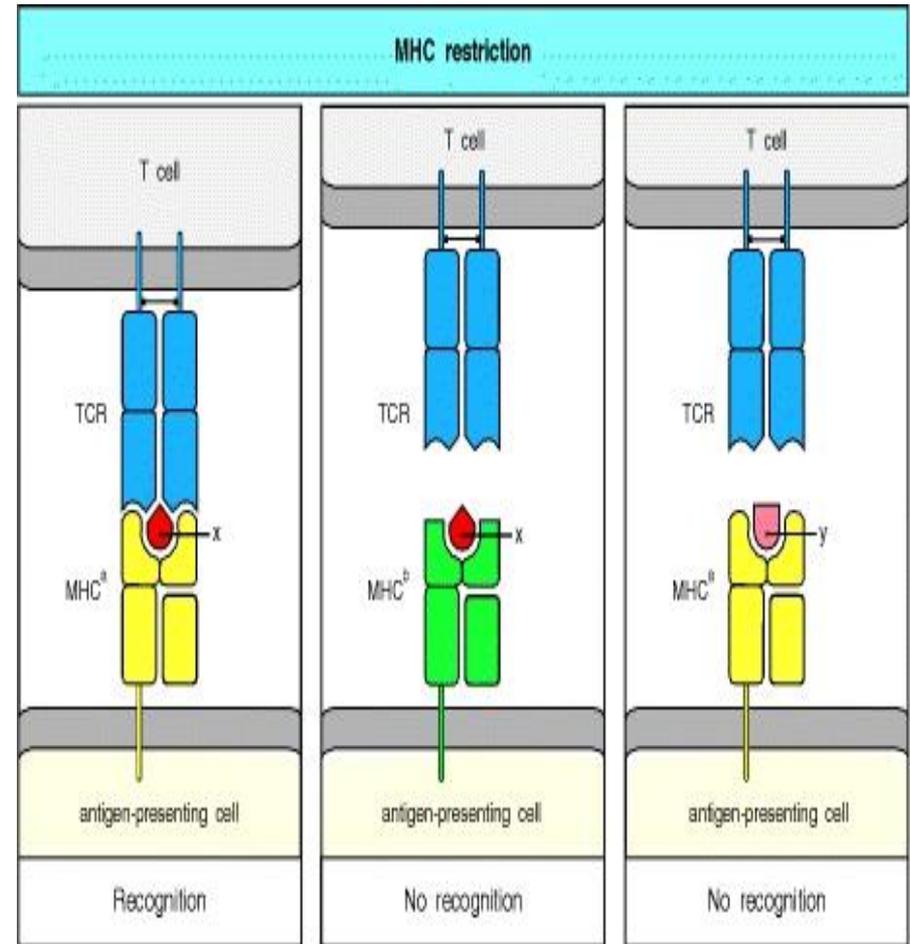


- Surface immunoglobulin (IGM or IGD) allows B cells to bind and internalize specific soluble intact antigen very efficiently. The internalized antigen is processed in intracellular vesicles where it binds to MHC class II molecules. These vesicles are then transported to the cell surface where the MHC class II:antigen complex can be recognized by Th2 cells. Because of high specificity, it is perfect when Ag concentration is low.



Inappropriate Ag or MHC

- CD4 bind MHC2 and CD8 bind MHC1
- TCR bind both the Ag and part of MHC
- Self Ag result in immature DC and macrophages (no co-stimulatory molecules)....T cell anergy.



CD4+ Th cells

- T cells with CD4 marker (glycoprotein) represent 70% of T cells in the periphery
- Play central role in modulating immunity via secretion of cytokines that modulate:
 - B cell activation (Th2)
 - Immunoglobulin secretion (Th2)
 - Macrophage and dendritic cell activation (Th1)
 - Cellular chemotaxis and inflammation (Th17)

Th1 or Th2 or TH17 cells

- **CD4+ T helper cells can be classified into 3 based on their cytokine profiles at time of activation of CD4 and type of antigen: T helper cell type 1 (Th1) and T helper cell type 2 (Th2). And TH17**

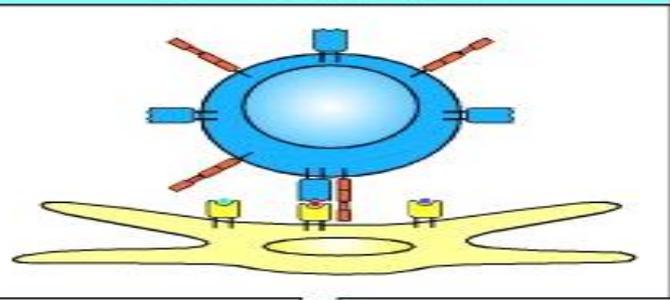
T cells differentiation; Effector CD4 cells

- Activated CD4+ helper T lymphocytes differentiate into
 - Th2 differentiations are mediated largely by
 - binding DC2 cells that engulf allergen or small extracellular microbe, soluble toxins, virus or worm
 - and the presence of IL-4 from DC2,
 - Th2 bind B cells and secrete cytokine to induce antibody production; IL-4 and IL-5 which activate B cell
 - Th1 differentiations are mediated by
 - binding Th to DC that secrete IL12 and IFN gamma,
 - intracellular pathogen multiplying within the macrophage's or DC vesicle after engulf infected cells,
 - Th1 produces IFN gamma
 - Th17; inflammatory DC secrete IL-6, TGF-beta in response to certain extracellular bacteria and fungi, TH17 survival needs IL23

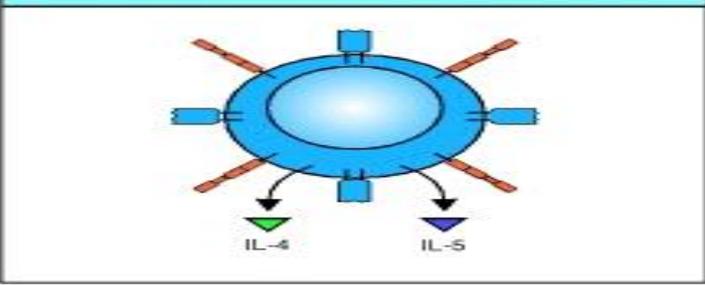
Antigen effect in priming TH1 or TH17 or TH2

- The nature and amount of ligand presented to a CD4 T cell during primary stimulation can determine its functional phenotype.
- CD4 T cells presented by DC cell with low levels of a small antigen or toxins or worms that bind the T-cell receptor less tightly, differentiate preferentially into TH2 cells making IL-4 and IL-5 and IL-13. Such T cells are most active in stimulating naive B cells to make antibody. Or activate eosinophils. the antigen is extracellular helminth or allergen
- T cells presented with a high density of a ligand that binds the T- cell receptor strongly differentiate into TH1 cells that secrete and IFN-gamma, and are most effective in activating macrophages. intracellular pathogen multiplying within the macrophage's phagosomes,

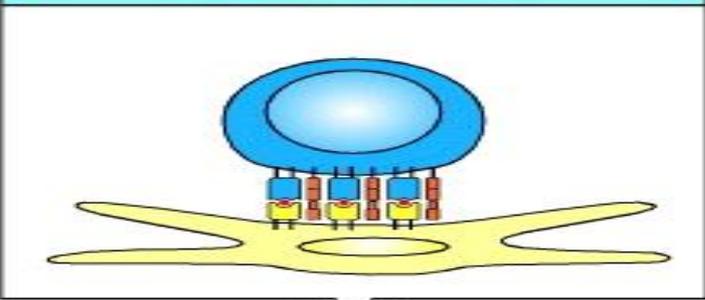
APC presents peptide with weak binding to the T-cell receptor



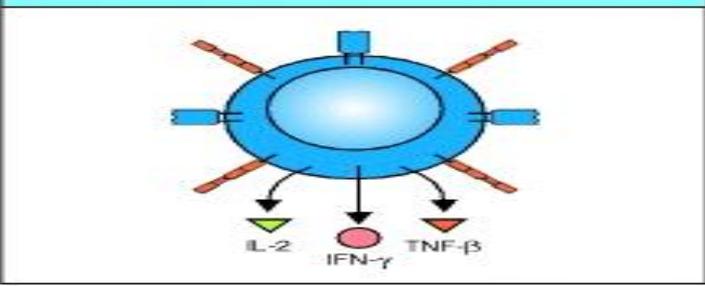
Naive CD4 T cell differentiates into T_H2 cell



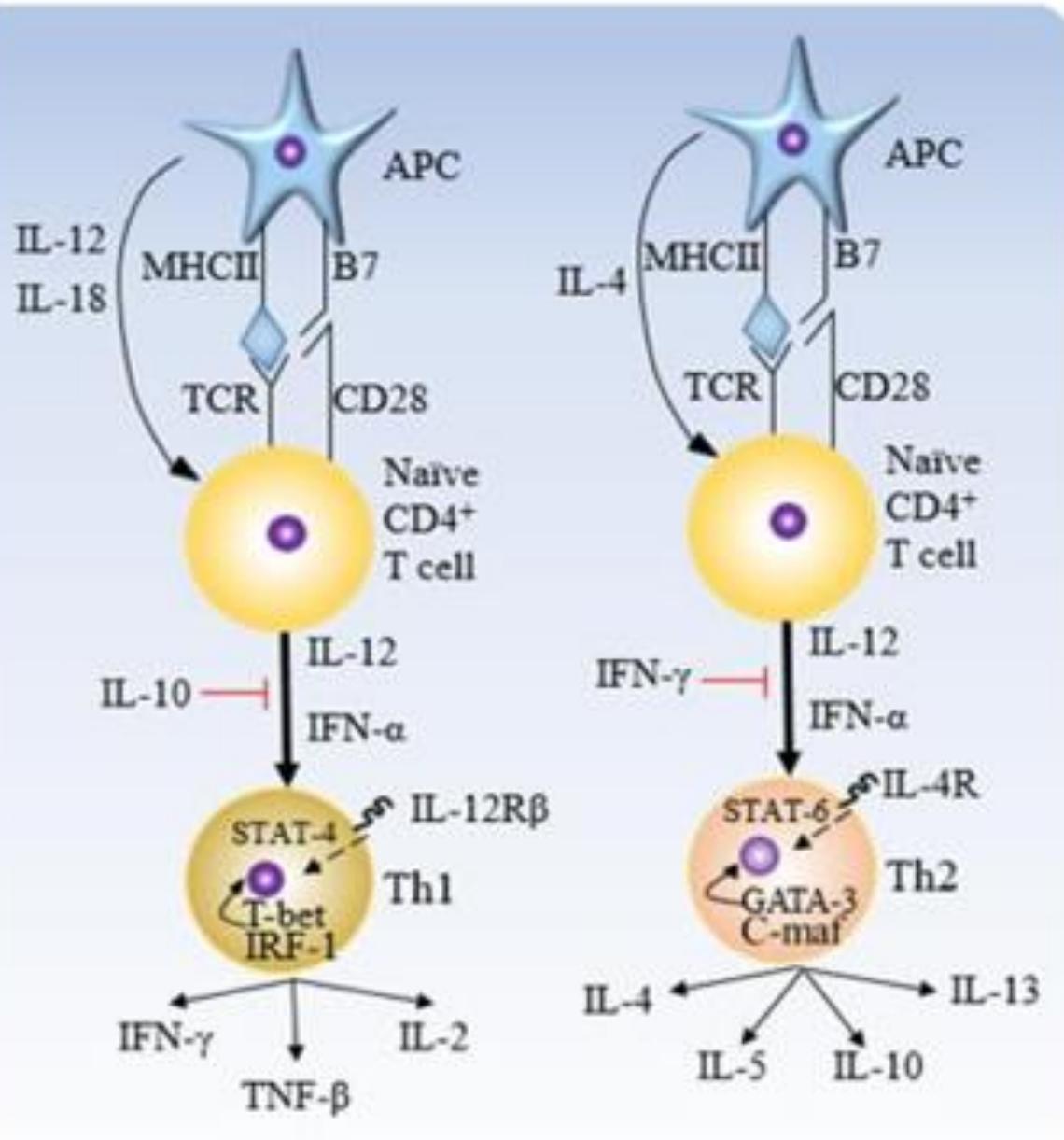
APC presents peptide that binds strongly to the T-cell receptor



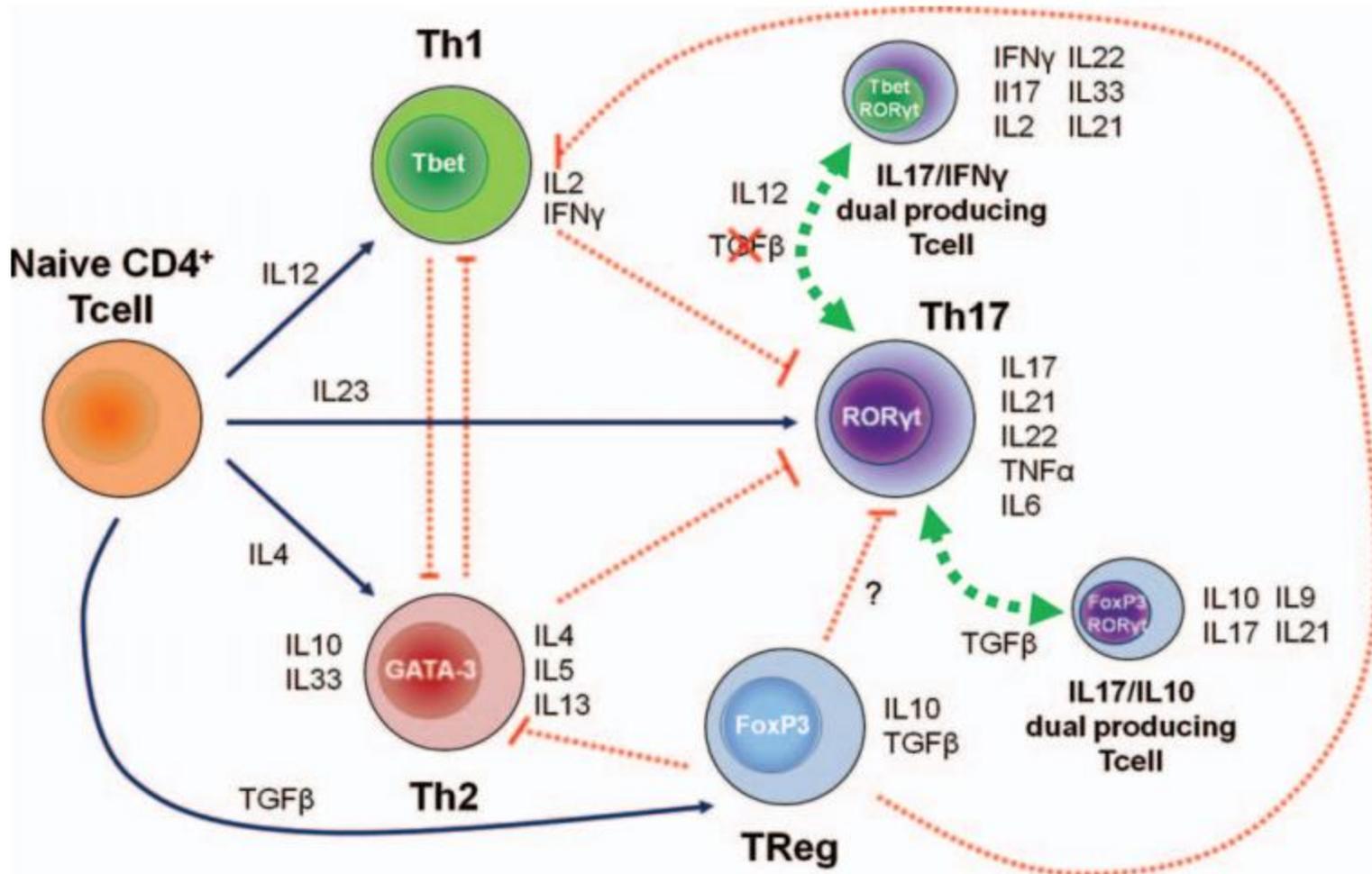
Naive CD4 T cell differentiates into T_H1 cell



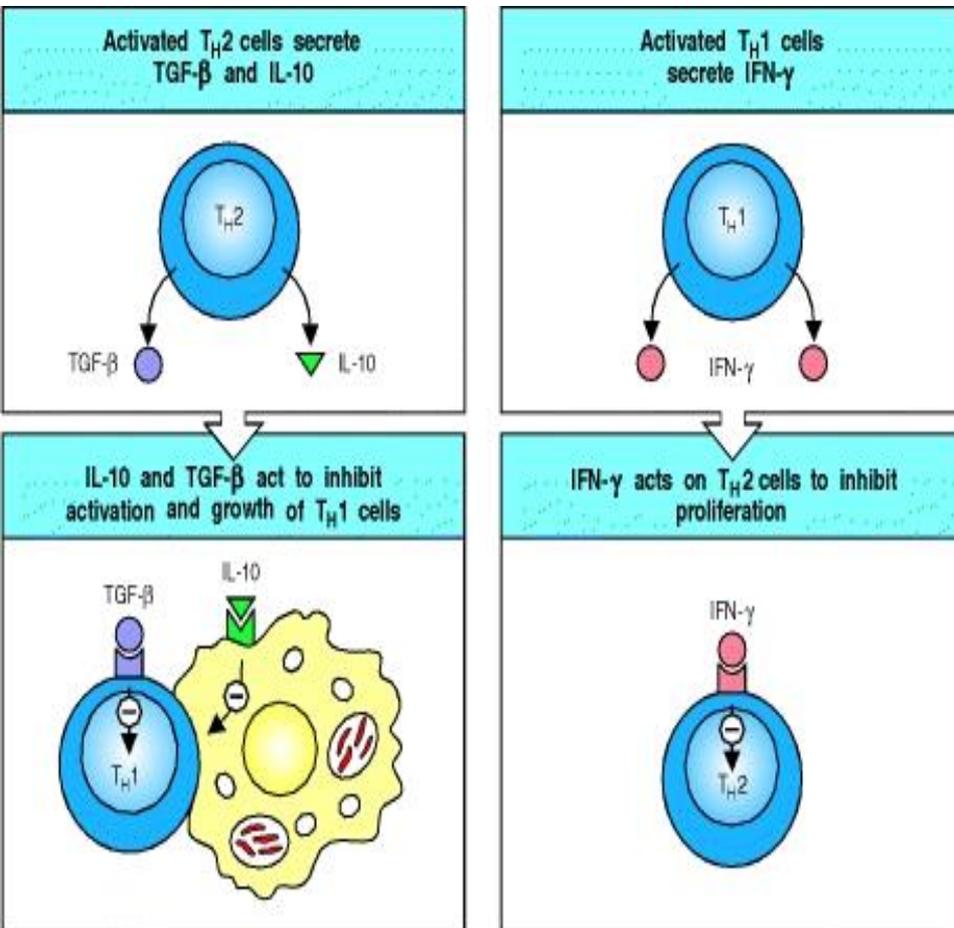
- Each subset of differentiated effector cells produces cytokines that promote its own development and may suppress the development of the other subsets
- IFN- γ secreted by TH1 cells promotes further TH1 differentiation and inhibits the generation of TH2 and TH17 cells.
- Similarly, IL-4 produced by TH2 cells promotes TH2 differentiation and inhibit TH1,
- and IL-17 produced by TH17 cells enhances TH17 differentiation.



Each subset inhibit other



Two subsets regulate each other

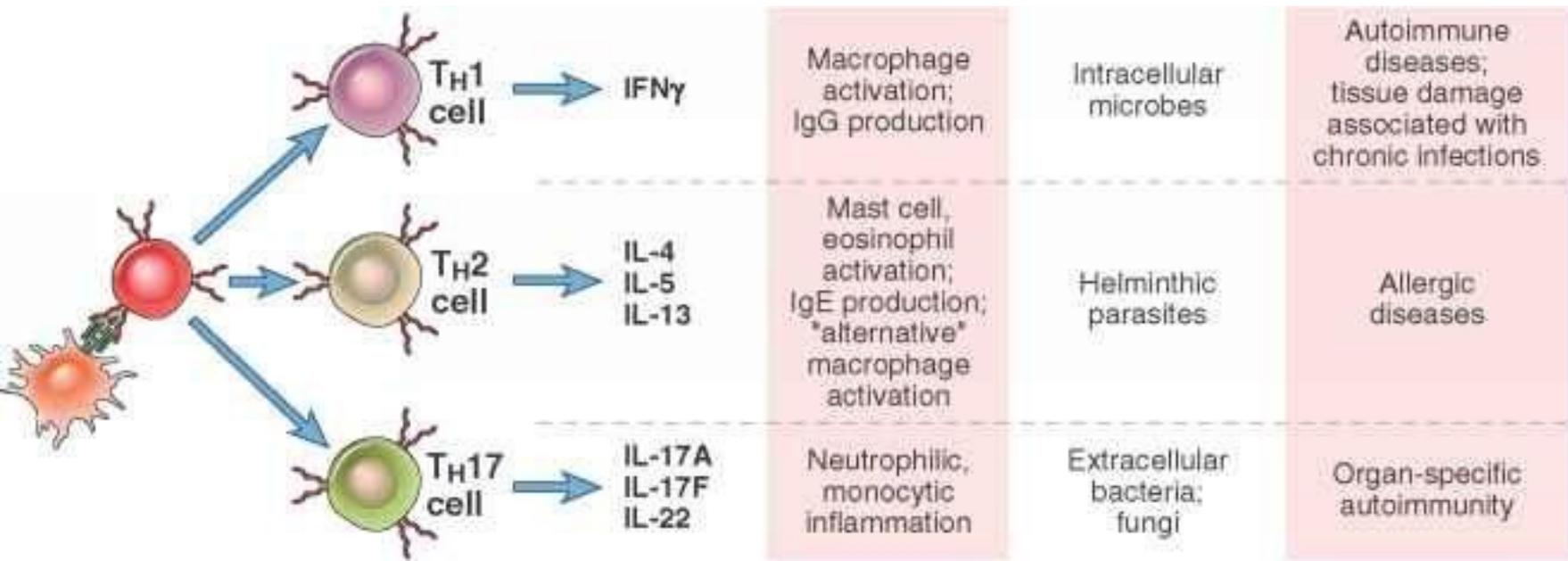


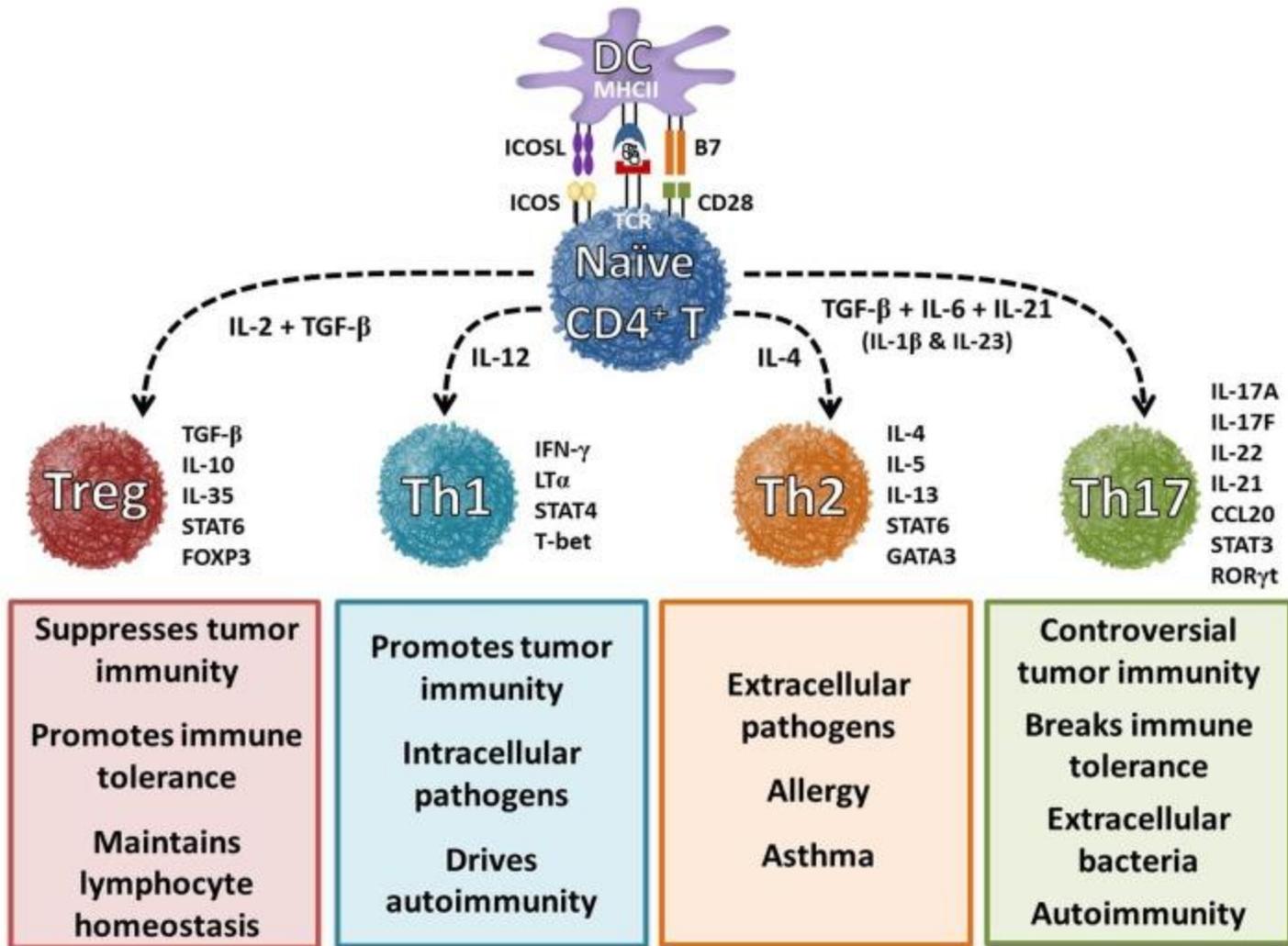
- TH2 cells make IL-4 which acts on macrophages to inhibit TH1 activation. Decrease auto-immunity
- TH1 cells make **IFN-γ**, which inhibit IL-4 and blocks the growth of TH2 cells (right panels). Decrease allergy
- These effects allow either subset to dominate a response by suppressing outgrowth of cells of the other subset. This help in using cytokines as therapy??.
- Balance toward TH1 help in cancer and allergy but increase autoimmunity
- Balance toward TH2 decrease autoimmunity
- TH17 helps in autoimmune diseases

CYTOKINES & DISEASE

Event	Development of tuberculoid leprosy	Development of lepromatous leprosy
T_H activation: cytokine production	Activation of T_H1 : production of IFN- γ	Activation of T_H2 : production of IL-4
Effector cell stimulation: effects on mycobacteria	Activation of macrophages: intracellular digestion of mycobacteria in cytoplasmic vesicles	Activation of B cells: antibodies have no access to intracellular mycobacteria
Resulting pathology	Some inflammatory tissue damage, but destruction of mycobacteria	Growth of mycobacteria and severe tissue damage

Table 3.3 The influence of cytokine production on disease pathogenesis following infection of macrophages by *Mycobacterium leprae*.





CD8 cells

- Activated CD8+ lymphocytes, cytotoxic T lymphocytes (CTL) result from infected or tumor antigen inside DC or infected cell (antigen multiply in cytosol) presentation and the presence of IL12 and IFN gamma.
- It kill cells harboring microbes as viruses or intracellular pathogen in the cytoplasm or cancer cells. By destroying the infected cells, CTLs eliminate the reservoirs of infection

Effector T cells

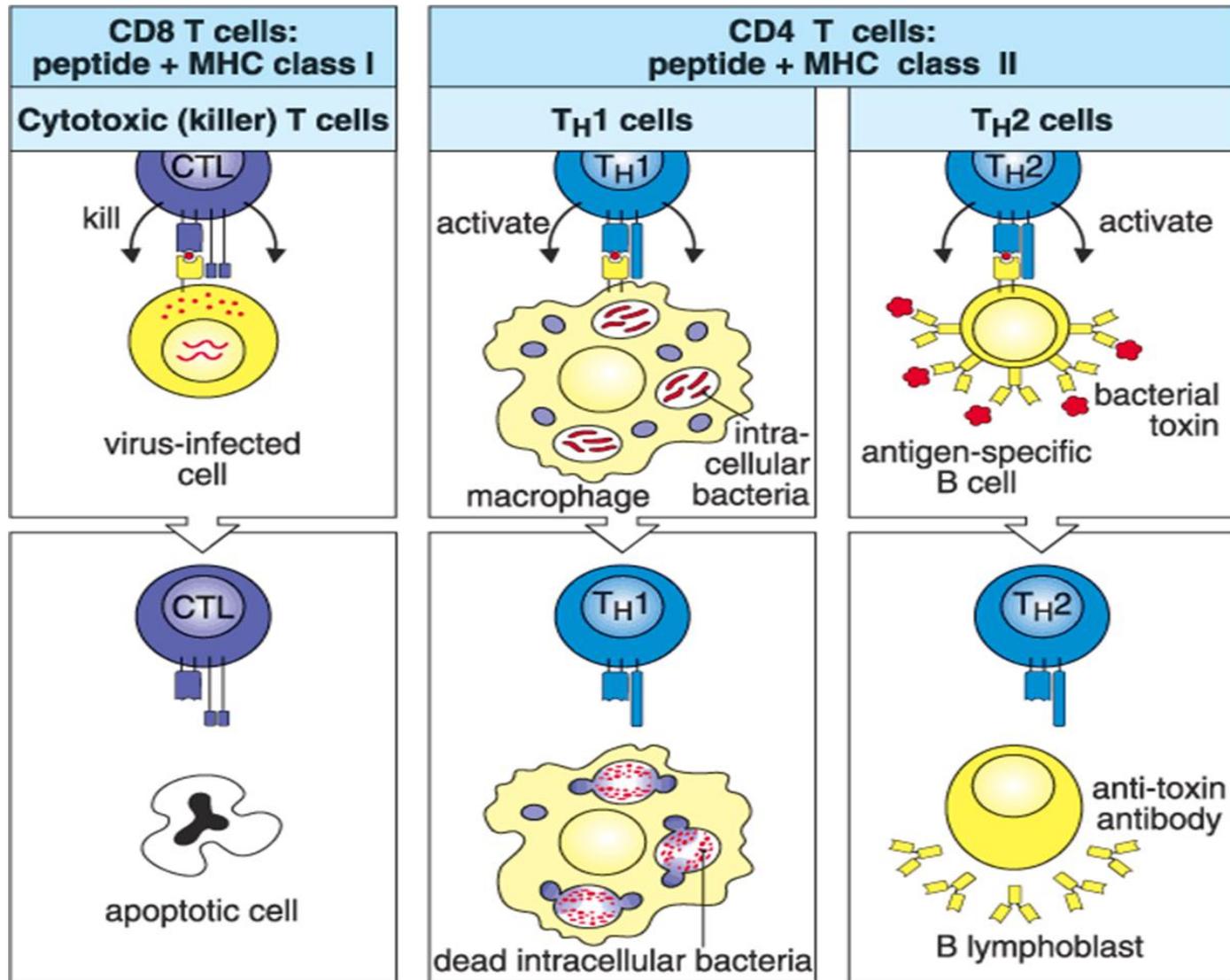


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